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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,629	04/02/2001	Heinz-Josef Lenz	13761-7001	8935

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EXAMINER

MYERS, CARLA J

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 03/14/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

09/824,629

Applicant(s)

LENZ ET AL.

Examiner

Carla Myers

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 1-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *Detailed Action*.

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1. Applicant's election with traverse of Group II, claims 13-30, in Paper No. 11 is acknowledged.

The traversal is on the ground(s) that restriction is only required when the inventions are independent and distinct. It is argued that the inventions are related to each other and thereby should be examined together. This argument is not found persuasive because dependent (i.e., related) inventions may be properly restricted if they are distinct. As discussed in MPEP 803, one of the two criteria for requirement of restriction is that the "inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed". Accordingly, the demonstration of distinctness of the inventions is sufficient grounds for restriction. As stated in MPEP 802.01

"(t)he law has long been established that dependent inventions (frequently termed related inventions) such as those used for illustration above may be properly divided if they are, in fact "distinct" inventions, even though dependent". Applicants further argue that the examiner has not provided any evidence that the claimed nucleic acids could be used for other purposes.

However, the examiner maintains that it would be clear to one of skill in the art that the nucleic acids could be used for the general purpose of detecting MnSOD variants. To further demonstrate the ability to use a nucleic acid as a means for detection, Ambrosone (reference "C2" in the IDS of Paper No. 8) is cited as teaching methods for detecting the -9 MnSOD allelic variant using primers which amplify MnSOD nucleic acids comprising the region that encompasses the -9 allelic variant. Ambrosone also teaches an association between the -9 MnSOD mutation and risk of breast cancer (see page 604).

The requirement is still deemed proper and is therefore made FINAL.

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2. Claims 13-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying increased risk of colon cancer in Hispanic subjects under the age of 35 wherein the methods comprise analyzing the nucleic acid of said subject and detecting the presence of a polymorphism in the MnSOD gene at the position encoding amino acid -9 of the MnSOD signal peptide, wherein when said subject is identified as being at increased risk of developing colon cancer when said subject is homozygous for the C allele at the nucleotide position encoding amino acid -9 of the MnSOD signal peptide, does not reasonably provide enablement for methods wherein any other alleles of the MnSOD gene are analyzed, methods wherein non-humans are diagnosed, or methods in which the subjects is not Hispanic or is over 35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 13-30 are drawn to methods for diagnosing colon cancer comprising determining the identity of an allelic variant of the MnSOD gene. The claims further include methods in which a region of the MnSOD gene including nucleotide 351 of SEQ ID NO: 1 is analyzed. The specification (see, for example, table 1) teaches only a single polymorphism in the gene encoding MnSOD, i.e. the mutation of a T to C at the nucleotide position encoding amino acid -9 of the MnSOD signal peptide, which corresponds to position 351 within the MnSOD fragment of SEQ ID NO: 1 and which results in a Val to Ala substitution in the MnSOD signal peptide. The specification teaches that in a sample population of Hispanics, the C/C genotype was present in

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38% of controls and in 38% of colon cancer patients; the C/T genotype was present in 48% of the controls and 45% of colon cancer patients; and the T/T genotype was present in 14% of controls and 17% of colon cancer patients. Accordingly, the results provided in the specification clearly teach that detection of the alteration of the MnSOD gene encoding amino acid -9 of the MnSOD signal peptide cannot be used to diagnose colon cancer in the general population since the mutation occurs at equal frequency in the control population and colon cancer patients. The specification further states that there is an association between risk of colon cancer and the stated mutation of the MnSOD gene in Hispanic individuals under the age of 35. In particular, the C/C genotype was found in 60% of colon cancer patients below the age of 35 and in 32% of colon cancer patients above the age of 35; the T/C and T/T genotypes together were present in 40% of the colon cancer patients below the age of 35 and in 68% of the colon cancer patients above the age of 35. Accordingly, the specification has enabled methods for identifying increased risk of colon cancer in Hispanic subjects under the age of 35 wherein the methods comprise analyzing the nucleic acid of said subject and detecting the presence of a polymorphism in the MnSOD nucleic acid encoding amino acid position -9 of the MnSOD signal peptide wherein when said subject is identified as being at increased risk of developing colon cancer when said subject is homozygous for the C allele. However, the specification has not enabled methods in which the presence of a C at position 351 of SEQ ID NO: 1 of the MnSOD gene is indicative of increased risk of colon cancer because no data is provided for the individual frequencies of the T/C versus T/T genotypes and there is no evidence to support the allegation that individuals heterozygous

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for the C allele are at an increased risk for having or developing colon cancer. In addition, the specification provides no evidence on the frequency of this MnSOD mutation in the general population. Given the unpredictability in the art of genetic diagnosis, one cannot extrapolate the findings obtained with a single ethnic group to the general population. In addition, the specification is not enabling for the detection of any additional mutations or polymorphisms in the MnSOD gene. The specification has taught a single mutation in the MnSOD gene, i.e. the alteration resulting in a Val to Ala substitution at amino acid position -9 in the signal peptide sequence of the MnSOD protein. The prior art of St. Claire teaches 3 polymorphisms in the promoter region of the MnSOD gene. The specification provides no guidance as to how to predictably identify additional polymorphisms in the MnSOD gene that would be expected to be associated with colon cancer. The ability to establish a correlation between the presence of a polymorphism and the occurrence of a specific disease is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. The specification provides no guidance as to how to apply the claimed method of diagnosis to the general population, to individuals above the age of 35 or to non-human subjects and provides no guidance as to how to practice the invention by detecting uncharacterized alterations in the MnSOD gene. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d

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833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate what additional polymorphisms may exist in the MnSOD gene which could be used to diagnose colon cancer and one cannot extrapolate the findings associated with a single polymorphism to other polymorphisms or to the general population. While one could contemplate a nucleotide substitution at each and every position in the MnSOD gene, such substitutions are not considered to be equivalent to specific polymorphisms associated with risk of colon cancer. Polymorphisms in the MnSOD gene associated with colon cancer represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type MnSOD gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. It is highly unpredictable as to which if any additional alterations in the MnSOD gene could be used to diagnose colon cancer. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

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3. Claims 13-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-23 are indefinite for failing to recite a final process step which agrees back with the preamble. The claims are drawn to methods for determining whether a subject has or is at risk of developing colorectal cancer. However, the claims recite a single step of determining the identity of the allelic variant in the MnSOD gene. Therefore, it is unclear as to whether the claims are intended to be limited to method for determining if a patient has or is at risk of having colorectal cancer or if the claims are intended to be limited to methods for detecting an allelic variant of the MnSOD gene. The claims should be amended to clarify the association between detecting the allelic variant and assessing risk of colorectal cancer.

Claims 13-23 are indefinite over the recitation of "the allelic variant" because this phrase lacks proper antecedent basis.

Claim 14 is indefinite over the recitation of "the subject's sample nucleic acid" because this phrase lacks proper antecedent basis. While the claim previously refers to nucleic acid obtained from the subject, the claim does not previously refer to the subject's sample nucleic acid. The phrase "the polymorphic region" also lacks proper antecedent basis. In addition, it is unclear as to whether the claim is intended to be limited to methods which detect variation specifically at nucleotide position 351 or if the method merely analyzes a region that

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encompasses the nucleotide at position 351. The claim is further indefinite because it does not clarify the relationship between SEQ ID NO: 1 and the MnSOD gene.

Claim 15 is indefinite over the recitation of “the polymorphic region” because this phrase lacks proper antecedent basis.

Claims 24-30 are indefinite over the recitation of “the subject’s cell sample” because this phrase lacks proper antecedent basis.

Claims 24-30 are indefinite for failing to recite a final process step which agrees back with the preamble. The claims are limited to methods for determining risk of colorectal cancer in a subject, yet recite a final step is one which correlates the base identity with risk of colorectal cancer. Therefore, it is not clear as to whether the method is intended to be one for determining an individuals risk for colorectal cancer or one for determining whether there is a correlation between a polymorphism and risk of colorectal cancer. It is also unclear as to whether the methods rely on the detection of a polymorphism at position 351 as indicative of risk of colorectal cancer or if the methods are intended to include analyzing any modification in a portion of the MnSOD gene that includes position 351 as defined in SEQ ID NO: 1 as indicative of risk of colorectal cancer.

Claims 28-30 are indefinite over the recitation of “the unaffected relevant population” because this phrase lacks proper antecedent basis.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 13 and 15, 16, 21 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by St. Clair (U.S. Patent No. 6,265,172).

St. Clair teaches methods for determining whether a subject is at increased risk for developing colon cancer wherein the method comprises detecting the presence of a mutation in the MnSOD gene as indicative of an increased risk for developing colon cancer (see columns 2 and 4). In particular, St. Clair teaches a polymorphism in the promoter region of the MnSOD gene which is associated with decreased MnSOD activity (see, for example, Figure 4 and column 4). The reference also teaches that detection of the polymorphism may be accomplished by PCR amplification followed by RFLP analysis or sequence analysis (columns 4-5). St. Clair also teaches the use of primers which are from 21-35 bp in length. Accordingly, the teachings of St. Clair anticipate the claimed invention.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-20 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over St. Clair in view of Cotton (Advances in Genome Biology (1991) Vol. 1, pages 253-300). St. Clair teaches methods for determining whether a subject is at increased risk for developing colon cancer wherein the method comprises detecting the presence of a mutation in the MnSOD gene as indicative of an increased risk for developing colon cancer (see columns 2 and 4). In particular, St. Clair teaches a polymorphism in the promoter region of the MnSOD gene which is associated with decreased MnSOD activity (see, for example, Figure 4 and column 4). The reference also teaches that detection of the polymorphism may be accomplished by PCR amplification followed by RFLP analysis or sequence analysis (columns 4-5). St. Clair also teaches the use of primers which are from 21-35 bp in length. St. Clair does not teach detecting the MnSOD mutation by methods which utilize SSCP, allele specific amplification, allele specific probes or an oligonucleotide ligation assay.

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Cotton teaches that mutations in a nucleic acid sample may be detected by a variety of methods including sequencing, RFLP analysis, allele specific amplification, allele specific oligonucleotide hybridization using labeled probes, SSCP analysis and ligation assays. The reference discloses that each of these methods is equally effective at detecting the presence of single base changes in nucleic acids.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of St. Claire so as to have detected the MnSOD mutation using the methods disclosed by Cotton of allele specific amplification, allele specific oligonucleotide hybridization using labeled probes, SSCP analysis or ligation assays in order to have provided an equally effective means for detecting the MnSOD mutation and diagnosing the risk of colon cancer.

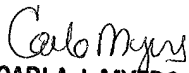
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703) 605-1237.

Carla Myers

March 13, 2002


CARLA J. MYERS
PRIMARY EXAMINER